foregoing amendments and following remarks, Applicants request reconsideration of the pending claims.

Claims 15-34 stand rejected under 35 U.S.C. §112, first paragraph for lack of enablement. Claims 15-34 stand rejected under 35 U.S.C. §112, second paragraph as being indefinite. Claims 15, 19, 20, 23, 25 and 29-34 are rejected under 35 U.S.C. §103(a) as being unpatentable over *Chaudhary* in view of *Bringman*. Claims 15, 19, 20, 23, 25 and 29-34 are further rejected under 35 U.S.C. §103(a) as being unpatentable over *Chaudhary* in view of *Bringman* and *Bram*. The Amendment filed March 19, 2001 is objected to under 35 U.S.C. §132 because the Examiner states it introduces new matter. Claims 15, 29, 30, 33 and 34 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite. Applicants will address each of these issues in the order presented in the Office Action.

35 U.S.C. §112, first paragraph (item #2)

The Examiner has rejected claims 15-34 under 35 U.S.C. §112, first paragraph on the basis that the specification does not reasonably provide enablement for "TACI" and "TACI-L." Applicants have amended the claims to delete reference to "TACI" and "TACI-L" and refer to the various polypeptides used in the screening assays in terms of amino acid sequences disclosed in SEQ ID NO:2 and 4.

The Examiner also asserts that the specification does not reasonably provide enablement for a polypeptide encoded by a nucleic acid molecule 75% identical to SEQ ID NO:1 or 3. In sum, the Examiner states that it would require undue experimentation for the skilled artisan to practice the invention as claimed. Applicants respectfully disagree and request the Examiner to reconsider this issue in light of the above amendments and following remarks.

The test of enablement is whether one reasonably skilled in the art could make and use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217, CAFC 1988). Applicants note that a patent need not teach, and preferably omits, what is well known in the art (*In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d1331, 1332 (Fed. Cir. 1991)). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue (*In re Angstadt*, 537 F.2d 498,504, 190 USPQ 214, 219 (CCPA 1976)). As to what constitutes undue experimentation, a factual determination of the factors described by the *Wands* Court is to be performed.

Applicants note that it is the claimed invention that must be enabled. The claimed method comprises a screening assay to identify test compounds that influence the interaction of TACI and TACI-L polypeptides. Applicants submit that one of skill in the

art would not have to undertake *undue* experimentation to practice the invention because screening assays involve well-established techniques and methodologies. Therefore, if any experimentation is required, it would be considered routine. As to whether the specification provides an enabling disclosure for TACI and TACI-L molecules, Applicants will address this issue in detail below.

The heart of the Examiner's rejection for lack of enablement for TACI and TACI-L variants lies in the assertion that the specification "does not identify those amino acid residues in the amino acid sequence of a TACI or TACI-L which are essential for their biological activity and structural integrity and those residues that are either expendable or substitutable." (page 3, second paragraph of Office Action). Applicants will show that the presently claimed invention is supported by an enabling disclosure and that one of skill in the art would be able to practice the claimed invention given the present disclosure as guidance.

Applicants disclose the polynucleotide and amino acid sequences for TACI and TACI-L (SEQ ID NO:1-4). The specification describes homologous analogs of TACI and TACI-L proteins having at least 75% identity at page 6, lines 4-26 and page 7, lines 10-27, respectively. Also, the specification teaches how to calculate percent identity and references a well-known and accessible computer program for doing so (page 6, lines 14-26), as well as standard techniques well known in the art, such as Southern hybridization methods (page 7, lines 22-24).

Importantly, all homologous analogs, fragments and soluble polypeptides must retain biological activity, which is defined at page 8, lines 3-4 as including the binding of TACI and TACI-L. This functional (and therefore structural) limitation permits one of skill in the art to identify those embodiments that satisfy the criteria of the claims, i.e., at least 75% identity and retaining the capacity to bind its cognate. The specification goes on to describe several techniques for analyzing the binding/interaction of TACI and TACI-L, as well as homologues, fragments, etc., using methods such as surface plasmon resonance, radioimmune based assays and fluorescence polarization binding assays (page 8, lines 10-18). These assays can be used to screen for biologically active TACI and TACI-L variants. Additionally, the specification provides working examples of cell-based assays for analyzing the interaction of TACI and TACI-L, which may be used to screen homologues, fragments and the like (Examples 4 and 5). It is important to note that the "first paragraph of 35 U.S.C. §112 requires nothing more than objective enablement; how such a teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance." *(In re Marzocchi and Horton*, 169 USPQ 364; CCPA 1971).

Applicants submit that the specification provides ample guidance and direction to one of skill in the art to practice the claimed invention. Applicants note that the test of

whether experimentation is undue is not merely quantitative, since a considerable amount of experimentation is allowed if it is routine (*In re Angestadt and Griffin*, 190 USPQ 214; CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 227 USPQ 4528; CAFC 1985). Applicants respectfully submit that identifying TACI and TACI-L variants that are at least 75% identical to the disclosed sequences that retain biological activity is considered routine experimentation. For example, one of skill in the art may perform site-directed mutagenesis on the disclosed TACI and TACI-L proteins and then screen the variants for the ability to bind to their respective binding partner by surface plasmon resonance, or screened for the ability to exert a "biological effect" (page 8, lines 5-9). Therefore, any experimentation required would not be considered undue because the art typically engages in such experimentation. Consequently, Applicants respectfully submit the rejection for lack of enablement may be properly withdrawn.

35 U.S.C. §112, second paragraph (item #3)

The Examiner has rejected claims 15-34 for reciting the terms TACI and TACI-L. The Examiner states that the specification does not identify the material element or combination of elements that is unique to, and therefore definitive of, "TACI" and "TACI-L" and therefore the metes and bounds of the claimed invention are not clearly set forth.

In response, Applicants have amended the claims to delete reference to "TACI" and "TACI-L" and refer to the various polypeptides used in the screening assays in terms of the amino acid sequences disclosed in SEQ ID NO:2 and 4. Also, Applicants have amended the specification to properly include the material incorporated by reference, as permitted under MPEP §608.01(p)(I)(A)(2). The definitions of TACI and TACI-L are unambiguously linked to the sequences of SEQ ID NO:2 and 4, respectively. As such, one of skill in the art would be able to determine the metes and bounds of the claimed invention.

Applicants have also amended the claims to more clearly define the present invention. Specifically, Claim 15 has been amended such that a protein (i.e., TACI) comprises a polypeptide selected from the group consisting of: (a) the polypeptide of SEQ ID NO:2; (b) a fragment of the polypeptide of SEQ ID NO:2; or (c) a polypeptide encoded by a nucleic acid sequence that is at least 75% identical to SEQ ID NO:1; wherein said polypeptides and fragments of (i) (a), (b) and (c) bind the extracellular domain of SEQ ID NO:4. And, a second protein (i.e., TACI-L) comprises a polypeptide selected from the group consisting of: (a) the polypeptide of SEQ ID NO:4; (b) a fragment of the polypeptide of SEQ ID NO:4; or (c) a polypeptide encoded by a nucleic

acid sequence that is at least 75% identical to SEQ ID NO:3; wherein said polypeptides and fragments of (ii) (a), (b) and (c) bind the extracellular domain of SEQ ID NO:2.

Claims 29-32 have been similarly amended to clearly define what comprises the polypeptides used in the screening assays. As such, all issues raised by the Examiner have been resolved and the rejections under 35 U.S.C. §112, second paragraph may be properly withdrawn.

35 U.S.C. §103(a) (item #4)

The Examiner has rejected claims 15, 19, 20, 23, 25 and 29-34 under 35 U.S.C. §103(a) as being unpatentable over *Chaudhary* in view of *Bringman*, and optionally, *Bram*. The Examiner states that it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to treat BJAB cells with TNRL1-α and assaying for cell survival, as taught by *Chaudhary*, and to make a neutralizing antibody, as taught by *Bringman*, against TNRL1-α bioactivity in the BJAB cell survival assay. The Examiner states that one of ordinary skill in the art would be motivated to make this modification because an antibody raised against a TNRL1-α binding site that neutralizes the cytotoxic activity of TNRL1-α would facilitate characterization and purification of TNRL1-α. Applicants respectfully traverse.

Applicants respectfully submit that the USPTO has not set forth a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP §2143.

Applicants emphasize that the cited references do not render the claimed invention obvious because one of skill in the art cannot develop screening methods based on a specific receptor-ligand interaction until that specific receptor-ligand relationship has been elucidated. Certainly, one of skill in the art would not have a reasonable expectation of success in developing such an assay until the specific receptor:ligand pair is known. Therefore, it was not until Applicants' discovery of the TACI-TACI-L relationship that a skilled artisan could develop the presently claimed invention.

Applicants submit that there is no suggestion in any of the references for the proposed combination. *Chaudhary* discloses the isolation and characterization of TNRL1-α (TACI-L) DNA and protein molecules. *Bram* teaches the isolation and

characterization of TACI DNA and protein molecules. *Bringman* describes the creation and characterization of an anti-lymphotoxin mAb that neutralizes the cytotoxic activity of lymphotoxin. Neither *Chaudhary* or *Bram* teach or suggest that their respective molecules are cognates of each other, nor do they teach or suggest the desirability of using the mAb of *Bringman* in screening assays to identify compounds that modulate the interaction of TACI and TACI-L. Similarly, *Bringman* does not describe the desirability of using a lymphotoxin-neutralizing mAb to develop a screening assay using the molecules of *Chaudhary* or *Bram*. Furthermore, *Bringman* does not provide any disclosure whatsoever on the use of antagonistic antibodies in screening assays.

In determining the differences between the prior art and the claims, the question under 35 U.S.C. §103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983). Also, "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

Applicants respectfully suggest that the Examiner has not viewed Applicants' invention as a whole and has inappropriately combined references that do not provide the requisite suggestion for the desirability of the combination. Importantly, the desirability of the combination must come from the prior art, not the Examiner.

Again, Applicants stress that it was not until Applicants' discovery of the TACI-TACI-L relationship that screening methods based on this receptor-ligand interaction could be developed. Certainly, one of skill in the art would not have a reasonable expectation of success in developing such an assay until the specific receptor:ligand pair is known.

Based on the above arguments, Applicants respectfully request the rejection of claims 15, 19, 20, 23, 25 and 29-34 under 35 U.S.C. §103(a) be properly withdrawn.

35 U.S.C. §132 (item #5)

The Examiner has objected to the amendment filed March 19, 2001 under 35 U.S.C. §132 for allegedly adding new matter. The Examiner notes that the material added to the specification should direct particular attention to the specific portions of the referenced documents where the subject matter being incorporated may be found. In response, Applicants have canceled the amendatory material of March 19, 2001 and have amended the specification to properly include the material incorporated by reference, as permitted under MPEP §608.01(p)(I)(A)(2). In addition, Applicants respectfully submit a Declaration executed by Applicants' representative stating that the amendatory material consists of the same material incorporated by reference in the referencing applications.

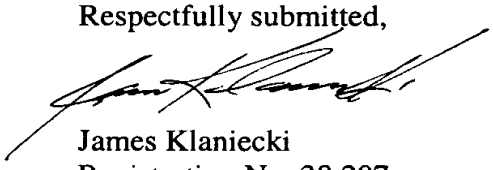
As such, Applicants have corrected all outstanding issues concerning the definitions of TACI and TACI-L.

35 U.S.C. §112, second paragraph (item #6)

The Examiner states that claims 15, 29 and 30 are indefinite for reciting "a protein comprising.... *fragments*" because the Examiner believes it is unclear whether the protein comprises continuous or discontinuous fragments. While Applicants do not agree with the Examiner's interpretation and characterization of the claims, Applicants are willing to amend the claims to facilitate prosecution. Thus, claims 15, 29, 30 and 31 have been amended to recite "a fragment" rather than "fragments," and as such, claims 33 and 34 have proper antecedent basis for "the fragment...." For the record, Applicants note that these amendments do not narrow the claims for reasons related to patentability.

Applicants respectfully request reconsideration and allowance of the pending claims. If any issues remain, the Examiner is cordially invited to call Applicants' representative to discuss resolution thereof.

Respectfully submitted,



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Date: Jan 16, 2002 Signed: Janet M. Kirtson

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of:	Raymond G. Goodwin and Wanwan S. Din	Docket No.:	2519
		Group Art Unit:	1647
Serial No:	09/302,863	Examiner:	D. Romeo
Filed:	April 30, 1999		

For: METHODS OF USE OF THE TACI/TACI-L INTERACTION

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

The paragraph at page 5, beginning at line 28 has been deleted and replaced with the following version:

-- The terms TACI and TACI protein are used interchangeably to describe the TNF receptor disclosed in WO 98/36361. As described in WO 98/36361 at page 19, lines 12-16, a TACI protein comprises a polypeptide having the amino acid sequence of SEQ ID NO:2 from residue 1 to residue 293. TACI proteins comprise an extracellular, transmembrane and cytoplasmic domain. The extracellular domain corresponds approximately to residues 1 to 166, inclusive, of SEQ ID NO:2, which contains a ligand binding domain, and the cytoplasmic domain corresponds approximately to residues 187 to 293, inclusive, of SEQ ID NO:2 (WO 98/36361 at page 18, line 17 to page 19, line 4). --

The paragraph at page 5, beginning at line 31 has been deleted and replaced with the following version:

-- "Fragments" of TACI comprise truncated amino acid sequences of SEQ ID NO:2 that retain the capacity to bind TACI-L (see below). In one embodiment, a TACI protein fragment comprises the soluble extracellular domain, which corresponds to the first amino acid of mature TACI to the transmembrane domain of the N-terminal portion of TACI. The ligand-binding region of TACI is a sub-fragment of the N-terminal fragment corresponding to the extracellular domain. One particular embodiment of the extracellular domain comprises amino acid residues 1 to 166, inclusive, of SEQ ID NO:2. In alternative embodiments, fragments of TACI comprise amino acid residues 1 to 166, inclusive, of SEQ ID NO:2 with one or more conservative substitutions (WO 98/36361 at page 18, line 16 to page 19, line 18 and page 33, line 33 to page 34, line 12). --

The paragraph at page 6, beginning at line 27 has been deleted and replaced with the following version:

-- The terms "TACI-L" and "TACI ligand" are used interchangeably to define the member of the TNF ligand family disclosed by WO 98/18921 and refer to a polypeptide having the amino acid sequence set forth in SEQ ID NO:4 or homologous analogs thereof (WO 98/18921 at page 7, line 25 to page 8, line 13). TACI-L is also disclosed as "TL5" in EP 0869180A1 and as "63954" in WO 98/27114. The full-length TACI-L comprises an extracellular domain, a transmembrane domain, and a cytoplasmic domain. Although the exact location of the extracellular, transmembrane, and cytoplasmic domains may differ slightly due to different analytical criteria for identifying the functional domains, the range of amino acids 1 to 46 generally represents the intracellular domain; amino acids 47 to 72 represent the transmembrane domain, and amino acids 73 to 285, the extracellular domain (WO 98/18921 at page 8, lines 2-13). --

In the claims:

15. (Twice Amended) A method of screening a test compound ~~to identify its ability to affect the interaction of TACI with TACI-L, the method~~ comprising the steps of:

a. forming a composition comprising (i) a ~~TACI~~ protein, ~~wherein said TACI protein comprises~~ comprising a polypeptide selected from the group consisting of:

(a) the polypeptide of SEQ ID NO:2;

(b) a ~~fragments~~ of the polypeptide of SEQ ID NO:2; or

(c) a polypeptide encoded by a nucleic acid sequence that is at least 75% identical to SEQ ID NO:1;

wherein said polypeptides and fragments of (i) (a), (b) and (c) bind ~~TACI-L~~ the extracellular domain of SEQ ID NO:4;

(ii) a ~~TACI-L~~ protein, ~~wherein said TACI-L protein comprises~~ comprising a polypeptide selected from the group consisting of:

(a) the polypeptide of SEQ ID NO:4;

(b) a ~~fragments~~ of the polypeptide of SEQ ID NO:4; or

(c) a polypeptide encoded by a nucleic acid sequence that is at least 75% identical to SEQ ID NO:3;

wherein said polypeptides and fragments of (ii) (a), (b) and (c) bind ~~TACI~~ the extracellular domain of SEQ ID NO:2; and

(iii) a ~~the~~ test compound; and

b. assaying for the level of interaction of the ~~TACI~~ protein of (i) and the ~~TACI-L~~ protein of (ii);

such that if the level obtained in step (b) differs from that obtained in the absence of the test compound, a test compound that affects the interaction of the ~~TACI~~ protein of (i) and the ~~TACI-L~~ protein of (ii) is identified.

29. (Amended) A method of screening a test compound ~~to identify its ability to affect the interaction of TACI with TACI-L, the method~~ comprising the steps of:

a. forming a composition comprising (i) a ~~TACI~~ protein~~, wherein said TACI protein comprises a polypeptide~~ selected from the group consisting of:

(a) the polypeptide of SEQ ID NO:2; and

(b) a fragments of the polypeptide of SEQ ID NO:2; wherein said fragments binds the extracellular domain of SEQ ID NO:4~~TACI-L~~;

(ii) the polypeptide of SEQ ID NO:4; and

(iii) a ~~the~~ test compound; and

b. assaying for the level of interaction of the ~~TACI protein~~ polypeptide of SEQ ID NO:2 or a fragment of the polypeptide of SEQ ID NO:2 and the polypeptide of SEQ ID NO:4~~the TACI-L protein~~;

such that if the level obtained in step (b) differs from that obtained in the absence of the test compound, a test compound that affects the interaction of the polypeptide of SEQ ID NO:2 or a fragment of the polypeptide of SEQ ID NO:2 and the polypeptide of SEQ ID NO:4 ~~TACI protein and the TACI-L protein~~ is identified.

30. (Amended) A method of screening a test compound ~~to identify its ability to affect the interaction of TACI with TACI-L, the method~~ comprising the steps of:

a. forming a composition comprising (i) the polypeptide of SEQ ID NO:2; (ii) TACI-L protein~~, wherein said TACI-L protein comprises a polypeptide~~ selected from the group consisting of:

(a) the polypeptide of SEQ ID NO:4; and

(b) a fragments of the polypeptide of SEQ ID NO:4; wherein said fragments binds ~~TACI-L~~ the extracellular domain of SEQ ID NO:2; and

(iii) ~~the~~ a test compound; and

b. assaying for the level of interaction of the polypeptide of SEQ ID NO:2~~TACI protein~~ and the ~~TACI-L protein~~ polypeptide of SEQ ID NO:4 or a fragment of the polypeptide of SEQ ID NO:4;

such that if the level obtained in step (b) differs from that obtained in the absence of the test compound, a test compound that affects the interaction of the polypeptide of SEQ ID NO:2 ~~TACI protein~~ and the ~~TACI-L protein~~ polypeptide of SEQ ID NO:4 or a fragment of the polypeptide of SEQ ID NO:4 is identified.

31. (Amended) A method of screening a test compound ~~to identify its ability to affect the interaction of TACI with TACI-L, the method~~ comprising the steps of:

a. forming a composition comprising (i) a fragments of the polypeptide of SEQ ID NO:2, wherein said fragments binds ~~TACI-L~~ the extracellular domain of SEQ ID NO:4;
(ii) a fragments of the polypeptide of SEQ ID NO:4, wherein said fragments binds ~~TACI~~ the polypeptide of SEQ ID NO:2; and
(iii) ~~the~~ a test compound; and

b. assaying for the level of interaction of ~~the TACI protein~~ a fragment of the polypeptide of SEQ ID NO:2 and ~~the TACI-L protein~~ a fragment of the polypeptide of SEQ ID NO:4;

such that if the level obtained in step (b) differs from that obtained in the absence of the test compound, a test compound that affects the interaction of a fragment of the polypeptide of SEQ ID NO:2, ~~the TACI protein~~ and a fragment of the polypeptide of SEQ ID NO:4~~the TACI-L protein~~ is identified.

32. (Amended) A method of screening a test compound ~~to identify its ability to affect the interaction of TACI with TACI-L, the method~~ comprising the steps of:

a. forming a composition comprising (i) the polypeptide of SEQ ID NO:2; (ii) the polypeptide of SEQ ID NO:4; and (iii) a ~~the~~ test compound; and

b. assaying for the level of interaction of the polypeptide of SEQ ID NO:2 ~~TACI protein~~ and the polypeptide of SEQ ID NO:4 ~~TACI-L protein~~;

such that if the level obtained in step (b) differs from that obtained in the absence of the test compound, a test compound that affects the interaction of the polypeptide of SEQ ID NO:2 ~~TACI protein~~ and the polypeptide of SEQ ID NO:4 ~~TACI-L protein~~ is identified.